REMARKS

Prior to the present Request for Continued Examination and Amendment and Response to Final Office Action ("Response"), Claims 1-2, 4-24 and 73-75 were pending. In this Response, applicants amend Claims 1, 8, 13, 73 and 75, and add new Claims 76-82. The claim amendments and new claims do not introduce any new matter. Claims 1-2, 4-24 and 73-82 will be pending after entry of the amendments.

Rejection under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejects Claims 1-2, 4-13, and 73-75 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

Claim 1 was amended in the previous Response to include the phrase "obtaining a mixture of high density lipoprotein particles and low density particles from a biological fluid." In the Final Office Action, the Examiner asserts that the specification only discusses obtaining the particles from blood plasma and does not provide sufficient written description for "biological fluids" in general. Applicants disagree. Applicants respectfully assert that, in addition to the examples describing how to obtain lipoprotein particles from blood plasma, an instance of a biological fluid, the specification describes various other biological fluids, for example, on p. 17, line 34, through p. 18, line 4. Based on the specification, one of ordinary skill in the art would know how to obtain lipoprotein particle derivatives recited in Claims 1-2, 4-13, and 73-75 from the biological fluids described on pp. 17-18 of the specification. Accordingly, applicants assert that the specification describes the subject matter of Claims 1-2, 4-13, and 73-75 in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully request that the rejection of Claims 1-2, 4-13, and 73-75 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. §102(b) as anticipated by Clay

The Examiner rejects Claims 1-2, 4-24, 74 and 75 under 35 U.S.C. § 102(b) as anticipated by Clay *et al.* (1999) "Formation of apolipoprotein-specific high-density lipoprotein particles from lipid-free apolipoproteins A-I and A-II." *Biochemical Journal*, v. 337, pp. 445-451 (hereinafter "Clay").

The Examiner asserts that, although the particles in Clay are obtained by a different process than the particles in the present application, the final product (HDL particles) is identical to the claimed particles comprising apoA-I. Applicants respectfully disagree. Applicants respectfully assert that the claimed particles are distinguished from the particles in Clay at least due to a number of structural differences discussed below. To support the assertions, applicants submit herewith a Declaration by one of ordinary skill in the art in the field of the present application ("the Declaration").

Clay investigated a possibility of formation of HDL by conjugation of apoA-I with lipids derived from other lipoprotein fractions (see Clay, p. 445, second column, end of the first paragraph). To this end, Clay examined formation of HDL particles from lipid-free apoA-I and apoA-II. In Clay, the lipid-free apoA-I and apoA-II were obtained from human plasma by sequential ultracentrifugation followed by solvent delipidation of the resulting HDL. The delipidation process used in Clay was performed at approximately 40:1 solvent to plasma ratio, repeated twice, as described in cited in Clay reference No. 21, Osborne, "Delipidation of Plasma Lipoproteins," *Methods in Enzymology*, v. 128, pp. 213-222 (1986) (of record in the present application). Solvent delipidation in Clay was followed by purification of apolipoproteins to homogeneity by anion-exchange chromatography on Q-Sepharose Fast Flow (see Clay, section *"Isolation of lipoproteins, apolipoproteins and LPL"* beginning on p. 445, second column, bottom). Clay described the resulting apoproteins as **"lipid free"** (see Clay, section *"Experimental conditions and processing of samples"* on p. 446, first column). Applicants respectfully bring to the Examiner's attention that their claimed particle derivatives are derived from **naturally occurring HDL particles.**

Applicants' particle derivatives are also referred to in the specification as "modified naturally occurring HDL particles" (see, for example, the specification, p. 18, line 38). Unlike the particles in Clay, applicants' particle derivatives are not based on lipid-free HDL-derived apoproteins. Clay does not teach particle derivatives based on naturally occurring HDL particles and does not anticipate the claims.

Clay teaches two series of experiments on formation of HDL lipoprotein particles from lipid-free apoproteins. The experiments result in three types of HDL particles (see Clay, section *"Experimental conditions and processing of samples"* on p. 446, first column). The first series of experiments was conducted with lipid-free apoA-II, and not apoA-I (*Id.*, first paragraph). Accordingly, the particles that Clay obtained in this first series of experiments fail to anticipate applicants' particle derivatives recited in the claims at least because these particles in Clay did not contain apoA-I.

In the second series of experiments in Clay, the particles were formed with lipid-free apoA-II in the presence or absence of apoA-I (*Id.*, second paragraph). The particles that were formed in the absence of apoA-I fail to anticipate the particle derivatives recited in the claims at least because these particles in Clay do not contain apoA-I.

In Clay, to form the particles obtained in the presence of apoA-I and apoA-II, the lipid-free apoproteins were incubated with low-density lipoprotein (LDL), and sodium oleate, followed by addition of albumin (*Id.*). The resulting pre-beta HDL particles included apoA-I/apoA-II particles and apoA-I particles. (see Clay, p. 449). Clay teaches in Table 2 on p. 450 the properties of the particle fraction that was isolated on an anti-apoA-I immunoaffinity column and included apoA-I and apoA-I/apoA-II particles.

Thus, in Clay, apoA-I and apoA-I/apoA-II particles were formed by incubation of lipid-free apoproteins and low density lipoproteins. As discussed above, applicants' claimed HDL particle derivatives are obtained by delipidation of the high density lipoprotein particles naturally occurring in a biological fluid, such as plasma. Accordingly, properties of particle derivatives recited in the claims are different from those of the reconstituted particles

in Clay at least because applicants' particle derivatives and the reconstituted particles in Clay are formed from different starting components. Applicants' claimed particle derivatives are also biochemically different from Clay's particles in several respects as discussed in the following paragraphs.

Clay's particles differ from applicants' claimed particle derivatives in their lipid composition. For example, the reconstituted particles in Clay do not contain measurable triacylglycerol or non-esterified fatty acids (see Clay, p. 449, second column). The particle derivatives in applicants' method are obtained by modifying naturally occurring HDL particles, which inherently contain a variety of lipids. The modification results in HDL particle derivatives that contain lower levels of at least one of phospholipids or cholesterol than the naturally occurring particles, but applicants' claimed particle derivatives contain levels of triacylglycerol (TG) comparable to those of the naturally occurring particles. Applicants' claimed particle derivatives also contain non-esterified fatty acids. See Section 5 and Exhibits C and D of the Declaration. Accordingly, applicants' claimed particle derivatives differ from the Clay particles for at least these reasons.

Applicants amend Claims 1, 13, and 75 to recite "wherein the particle derivative has a lower content of at least one of the phospholipids or cholesterol." Support for the amendment is found throughout the specification, for example, on pp. 38-39 in Examples 2 and 3. Applicants add new Claims 77 and 81 that recite triglycerides and fatty acids. New Claim 77 is based on previously presented Claim 1. New Claims 77 and 81 are supported in the specification, for example, on p. 18, lines 6-12. Applicants respectfully assert that Clay does not teach the particle derivatives recited in the amended claims and does not anticipate the claimed particles.

Clay's particles also differ from applicants' particle derivatives in their protein composition. As discussed above, the HDL particles generated in Clay were formed using lipid-free apoA-I and apoA-II, and incubating them with LDL. Accordingly, the only protein components in the Clay apoA-I-containing HDL particles are apoA-I and, optionally, apoA-

II. Clay does not disclose any other apolipoproteins in its reconstituted HDL particles. Clay also fails to teach a method of generating HDL particles comprising apolipoproteins other than apoA-I or apoA-II. In contrast, applicants' claimed delipidated HDL particles inherently retain similar composition and distribution of apolipoproteins to those found in the HDL particles found in the biological fluids. In particular, in addition to apoA-I and apoA-II, applicants' particles comprise at least apoC-III, apoD, or apoE. See Section 6 and Exhibit C of the Declaration. Applicants assert that Clay fails to anticipate applicants' claimed particle derivatives because Clay does not disclose HDL particles with naturally occurring apolipoprotein composition. Applicants also add new Claims 76, 78-80 and 82 that recite "at least one of apolipoprotein C-III, apolipoprotein D, or apolipoprotein E." Support for the amendment is found in the specification, for example, on p. 2, lines 27-30 and p. 19, lines 7-10. Clay fails to teach the protein components of the particles recited in the new claims and fails to anticipate the claims for at least this reason.

Clay's particles differ from applicants' particle derivatives in their apoA-I/apoA-II ratio. In Table 2, Clay teaches the results of characterization of its apoA-I containing HDL particles (see p. 450 in Clay). Applicants respectfully assert that Clay's particles possessing the characteristics disclosed in Table 2 are different from applicants' particle derivatives. First, according to the results of two experiments reported in Table 2, Clay's particles have apoA-I/apoA-II stoichiometric molar ratios of 1.8 and 2.9, that is, an average of approximately 2.3. In contrast, applicants' particle derivatives inherently possess an apolipoprotein composition similar to that of naturally occurring particles and have an apoA-I/apoA-II stoichiometric molar ratio of 3.0, similar to that of intact plasma. See Section 7 and Exhibit C of the Declaration. Applicants assert that Clay fails to anticipate the claimed particles because Clay fails to teach HDL particles with a naturally occurring apoA-I/apoA-II molar ratio. Thus, Clay's particles are different from applicants' claimed particle derivatives and Clay fails to anticipate the claims for at least the reasons discussed above.

In view of the foregoing, applicants respectfully assert that the rejection of Claims 1-2, 4-24, 74 and 75 under 35 U.S.C. § 102(b) as anticipated by Clay has been overcome and request its withdrawal.

Rejection under 35 U.S.C. §102(b) as anticipated by Durbin

The Examiner rejects Claims 1-2, 4-24, 74 and 75 under 35 U.S.C. § 102(b) as anticipated by Durbin and Jonas (1999) "Lipid-free apolipoproteins A-I and A-II promote remodeling of reconstituted high density lipoproteins and alter their reactivity with lecithin:cholesterol acyltransferase." *Journal of Lipid Research*, v. 40, pp. 2293-2303 (hereinafter "Durbin").

The Examiner asserts that the lipoprotein particles in Durbin anticipate the claimed particles. Applicants respectfully disagree. Applicants respectfully assert that the claimed particle derivatives are distinguished from the particles in Durbin at least due to a number of structural differences discussed below. In support of their position, applicants submit herewith a Declaration by an expert in the field of lipid studies ("the Declaration").

Durbin reports the effect of lipid-free apoA-I and apoA-II on the structure and properties of **reconstituted** HDL particles. In Durbin, the particles are reconstituted from human plasma-derived apoA-I or apoA-II with L-a-palmitoyloleoylphosphatidylcholine (POPC) and cholesterol (see Durbin, p. 2294, second column, section *"Preparation of rHDL"*).

The particles in Durbin are generated using POPC and lipid free apoA-I and lipid free apoA-II. Accordingly, the particles in Durbin contain only POPC and cholesterol as their lipid components. Thus, the Durbin particles contain **a single phospholipid** – POPC. Unlike the Durbin particles, applicants' claimed particle derivatives contain **phospholipids**, comprising at least one of phosphatidylcholine (PC), phosphatidylserine (PS) or phosphatidylethanolamine (PE). See Section 8 and Exhibit D of the Declaration.

In view of the foregoing, applicants assert that Durbin fails to teach the particle derivatives recited in the claims and does not anticipate the claims. Applicants request that the rejection of Claims 1-2, 4-24, 74 and 75 under 35 U.S.C. § 102(b) as anticipated by Durbin be withdrawn.

Double Patenting

The Examiner provisionally rejects Claims 1-2, 4-24, 74 and 75 under the judicially created doctrine of obviousness-type double patenting as unpatentable over Claims 73-77 and 80 of the co-pending applicants U.S. Patent Application No. 10/996,570. If the rejection applies when allowable subject matter is found, applicants will address this rejection by filing an appropriate terminal disclaimer.

CONCLUSION

The foregoing is submitted as a full and complete response to the Final Office Action mailed September 9, 2005. No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies which may be required or credit any overpayment to Deposit Account Number 11-0855.

Applicants assert that the claims are in condition for allowance and respectfully request that the application be passed to issuance. If the Examiner believes that any informalities remain in the case that may be corrected by Examiner's amendment, or that there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned agent at (404) 815-6102 or to Dr. John McDonald at (404) 745-2470 is respectfully solicited.

Respectfully submitted,

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